REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1 to 11 and 23 are pending. Claims 12 to 22 have been canceled. New claim 23 has been added. No new matter has been added by the present amendment.

The Objections to Claims 4 and 5

The misspelling of IGF-IR has been corrected in claims 4 and 5, and so it is requested that the objection be withdrawn.

The Biological Deposit Rejection

Claim 10 is rejected for lack of enablement. In response, the specification has been amended to include the address of the depository. Further, applicants' representative declares that a deposit of the claimed materials (<IGF-1R> HuMab Clone 1a, <IGF-1R> HuMab Clone 23 and <IGF-1R HuMab Clone 8) has been made under the Budapest Treaty at the Deutsche Sammlung von Mikrooganismen und Zelkulturen GmbH, with an address of Mascheroder Weg 1b, D-38124 Braunschweig, Germany. The <IGF-1R> HuMab Clone 1a has been accorded accession number DSM ACC2586, <IGF-1R> HuMab Clone 23 been accorded accession number DSM ACC2588, and <IGF-1R HuMab Clone 8 been accorded accession number DSM ACC2589. All restrictions on the availability to the public of the deposited material will be irrevocably removed upon granting of a patent. Further, the material has been deposited under conditions that ensure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 CFR 1.14 and 35 U.S.C. § 122. The deposit receipts for <IGF-1R> HuMab Clone 1a, <IGF-1R> HuMab Clone 23 and <IGF-1R HuMab Clone 8 are submitted herewith (Tab 1). It is respectfully submitted that the above amendments, declaration, and submission of the deposit receipts overcome the ground for rejecting claim 10 for lack of enablement, and it is respectfully requested that the rejection be withdrawn.

Rejection of Claims 6 to 9 Under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 6 to 9 for lack of enablement, asserting that the specification does not enable how to make and use the claimed antibodies with the recited possible variations in amino acid sequences. This rejection is traversed, and reconsideration is requested.

The Examiner has asserted that only the antibody termed "1A" is enabled. It appears that the Examiner has not appreciated that the amino acid sequences for antibodies 8 and 23 are also fully disclosed. SEQ ID NO:3 and SEQ ID NO:4 are the heavy and light chains of antibody 8, and SEQ ID NO:5 and SEQ ID NO:6 are the heavy and light chains of antibody 23. The "substitutions and deletions" cited in the office action by the Examiner are in fact those that distinguish antibodies 1A, 8, and 23 from each other. In essence, antibodies 8 and 23 are variants of antibody 1A, differing in the amino acid options recited in claim 6 and those dependent thereon. Thus, it is respectfully submitted that the rejection of claims 6 to 9 for lack of enablement should be withdrawn.

Rejection of Claims 1 to 11 Under 35 U.S.C. § 112, first paragraph

Claims to 1 to 11 were rejected for lack of enablement.

The Examiner has rejected claims 1 to 10 for lack of enablement. As an initial note, applicants dispute the Examiner's contention that "The claims encompass the experimental and unpredictable field of *in vivo* therapy for cancer." All of the pending claims are directed to compositions of matter, not methods for the *in vivo* treatment of cancer. This is not a proper ground for rejection, as it is factually incorrect.

Claims 1, 2, 4, and 5 stand rejected for lack of enablement. This rejection is respectfully traversed, and reconsideration is requested.

Claim 1 recites: (1) a human or humanized antibody which binds to IGF-IR (2) where the antibody inhibits the binding of IGF-I and IGF-II to IGF-IR (3) where the antibody is of a IgG1 isotype (4) where the antibody shows a ratio of inhibition of the binding of IGF-I and IGF-II to IGF-IR of 1:3 to 3:1, and (5) where the antibody induces cell death of 20% or more cells of a preparation of IGF-IR expressing cells after 24

hours at a concentration of 100 nM of the antibody in an antibody dependent cellular toxicity assay.

It is indisputable that an antibody that binds to IGF-IR is described and enabled. The USPTO written description guidelines state that:

> Considering the routine art-recognized method of making antibodies to fully characterized antigens, the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature, one of skill in the art would have recognized that the spectrum of antibodies which bind to antigen X were implicitly disclosed as a result of the isolation of antigen X.

This excerpt from the written description guidelines begins with the recognition that it is routine in the art to make antibodies to a fully characterized antigen, and concludes that "the spectrum of antibodies which bind to antigen X were implicitly disclosed as a result of the isolation of antigen X."

The IGF-IR was known and characterized prior to applicants' filing date, and so antibodies to IGF-IR are described and enabled. It was known in the art how to make human or humanized antibodies. When making such human or humanized antibodies, the isotype is predetermined. The present specification provides assays to determine whether and with what affinity an antibody binds to the IGF-IR (Example 2), and an assay for the IC50 concentration for inhibition of IGF-I and IGF-II binding (Example 7). Methods for determining ADCC and CDC activities are set forth in Example 15.

Thus, making antibodies according to the claims would be routine for one of ordinary skill in the art, given the disclosure of the present specification. Although screening and assaying for the various properties set forth in the claims might be time consuming, this does not rise to the level of "undue experimentation." In *Wands*, it was a similar screening process that was found NOT to be undue experimentation. Accordingly, the rejection of claims 1, 2, 4, and 5 for lack of enablement should be withdrawn.

With respect to the alleged lack of enablement of claims 6 to 9, applicants have detailed above the Examiner's misunderstanding of the scope of disclosure of the specification. The complete sequences of the heavy and light chains of all of antibodies 1A, 8, and 23 are disclosed in the specification. Further, cell lines producing these antibodies have been deposited under the Budapest Treaty. The specific amino acid variations for heavy and light chains recited in claims 6 to 9 have been tested, as they are those present in antibodies 8 and 23,. These specifically detailed modifications from the sequences of antibody 1A, as embodied in antibodies 8 and 23, have been shown not to abolish binding to the IGF-IR (see Example 2). Thus, the Examiner's comments regarding what the literature says about the unpredictable effects of variable chain amino acid changes are inapposite, as the claimed modifications have been shown to be functional. Accordingly, claims 6 to 9 are respectfully submitted to be fully enabled, and the rejection of claims 6 to 9 for lack of enablement should be withdrawn.

The rejection of claim 10 should be withdrawn as the cells lines producing the antibodies recited in the claim have been deposited under the Budapest treaty, as detailed above.

Claim 11 has been amended, and recites "A composition comprising the antibody of claim 1 and a pharmaceutically acceptable carrier or diluent." New claim 23 echoes this structure, but is dependent on claim 6. It is respectfully submitted that the amendments overcome all of the grounds for rejection of claim 11 proffered by the Examiner. Claim 11 does not encompass "*in vivo* therapy for treating a large number of diseases." Claims 11 and 23 are composition claims, not method claims. The appropriate question for enablement is, can the claimed compositions be made, and can they be used, by one of ordinary skill in the art based on the disclosure of the present specification. It is respectfully submitted that one of ordinary skill in the art, given the present disclosure, could make a formulation of an antibody of the invention with a pharmaceutically acceptable carrier or diluent. Further, it is submitted that one of ordinary skill could easily use, i.e., administer, such a composition to a subject, given the present disclosure. Such administration could be, e.g., in a clinical trial setting, where a formulation with pharmaceutically acceptable excipients would be required for

human administration.Thus, the rejection of claim 11 for lack of enablement should be withdrawn.

Rejection of Claims 1 to 11 Under 35 U.S.C. § 112, second paragraph

Claims 1 to 11 have been rejected for indefiniteness. This rejection is respectfully traversed, and reconsideration is requested.

Claim 1 has been amended to make explicit what was otherwise implicit from the specification, i.e., that inhibition of binding of IGF-I and IGF-II is expressed as IC50 values (see Example 7). Claim 1 recites that, *inter alia*, the antibodies of the invention should have a ratio of IC50s for the inhibition of the binding of IGF-I and IGF-II to IGF-IR of 1:3 to 3:1. The Examiner's stated ground for the indefiniteness rejection is "...the claim does not teach the method for obtaining the ratio of inhibition. The claims is incomplete for omitting essential steps." It is respectfully submitted that it is not the job of the claims to "teach" anything. Claims recite limitations, which need to be supported by the specification. Claim 1 recites the above IC50 ratio limitation. Example 7 teaches how to assay antibodies for their IC50s with respect to inhibition of the binding of IGF-I and IGF-II to IGF-IR. This is all that 35 U.S.C. § 112, second paragraph requires. According, the ground for rejection has been overcome, and the rejection should be withdrawn.

Rejection of Claims 1 and 3 to 5 Under 35 U.S.C. § 102(a)

Claims 1 and 3 to 5 stand rejected as anticipated by Li et al. ("Li"). The Examiner has cited various disclosures of Li as meeting the limitations of claims 1 and 3 to 5. However, the Examiner has not shown where Li meets limitation (c) of claim 1, which is also incorporated into claims 3 and 5. Li discloses αIGF-IR scFv and αIGF-IR scFv-Fc. The αIGF-IR scFv cannot induce antibody dependent cellular toxicity because it lacks the Fc effector region that is required for such activity. With respect to αIGF-IR scFv-Fc, in a later paper by Li and others, *Cancer Research*, 63:627-635 (Feb 1, 2003) (submitted herewith, Tab 2), it is stated by the authors that αIGF-IR scFv-Fc does not induce ADCC by natural killer cells (see heading of last paragraph on page 630). Since

the antibody stated by the Examiner to anticipate claims 1 and 3 to 5 does not meet, *inter alia*, limitation (c) of claim 1, claim 1 and all claims dependent therefrom cannot be anticipated by the antibody of Li, and it is respectfully requested that the rejection be withdrawn.

Rejection of Claims 1, 2, 6, and 11 Under 35 U.S.C. § 103(a)

Claims 1, 2, 6, and 11 stand rejected as obvious over the combined disclosures of Li, Bruggemann, and Cohen. The rejections are respectfully traversed, and reconsideration is requested.

The rejection of claim 6 is most clearly incorrect. Claim 6 requires, *inter alia*, an antibody comprising a heavy chain having CDRs comprising CDR1 (aa 31 to 35), CDR2 (aa 50-66), and CDR3 (aa 98-108) wherein amino acid 31 can be asparagine or serine, amino acid 66 can be glycine or can be deleted, and amino acid 104 can be glutamic acid or aspartic acid, and an antibody light chain having CDRs comprising CDR1 (aa 18-34 or aa 24-34), CDR2 (aa 50-56) and CDR3 (aa 89-98) of SEQ ID NO:2, wherein amino acid 96 can be proline or isoleucine, and amino acid 98 can be phenylalanine or can be deleted.

The Examiner has stated that "Cohen et al. teach an IGF-IR antibody comprising a heavy chain with the amino acid sequence NO:6, which has 100% identify with SEQ ID NO:2 of this instant application, and light chain encoded by amino acid SEQ ID NO:16, which has 100% sequence identity with SEQ ID NO:2 of the instant application (column 16, lines 28-38)." Applicants respectfully request that the Examiner reexamine the sequences which he asserts to be identical, as it is respectfully submitted that SEQ ID NO:6 of Cohen differs from SEQ ID NO:2 of the present application at amino acids 7, 30, 32, 34, 41,46, 53, 55, 56, 70, 89, 91, 96, 97, 100, 104, and 105. Amino acids 30, 32, 34, 53, 55, 56, and 89, 91, 96 and 97 are within the light chain CDRs required by present claim 6. Similarly, heavy chain SEQ ID NO:16 of Cohen differs from SEQ ID NO:1 of the present application at amino acids 5, 6, 13, 24, 30, 31, 35, 52, 54, 57, 58, 74, 77, 90, 97, and 114, and in particular in CDR3, where the only amino acid common between the Cohen CDR and CDR3 of SEQ ID NO:1 is amino acid 104 (asp). In light of

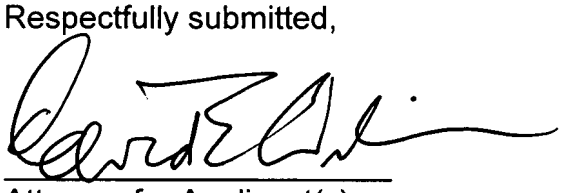
these significant differences, nowhere disclosed or suggested by any of the cited prior art, it is respectfully submitted that claim 6 cannot properly be said to be obvious in view of the cited prior art, and the rejection should be withdrawn.

With respect to claims 1, 2, and 11, the deficiency of Li, discussed above with respect to the anticipation reference, is also fatal to an obviousness determination based on Li. The Li αIGF-IR scFv-Fc antibody is an IgG1 type, yet does not induce ADCC. Bruggemann discloses IgG1 antibodies that have ADCC inducing activity, but these antibodies are not specific for the IGF-IR. Thus, although some IgG1 antibodies can induce ADCC, per Bruggemann, there is no disclosure in the cited prior art of an IGF-IR antibody that induces ADCC, nor is there any reason, based on any of the cited prior art, for one of ordinary skill to generate or screen for an IGF-IR antibody with such activity. In light of the failure of any of the cited prior art to comment on the desirability or undesirability for an IGF-IR antibody to have ADCC inducing activity, it is respectfully submitted that the prior art cannot be said to render claims 1, 2, and 11 obvious, and so the rejection of these claims for obviousness should also be withdrawn.

In light of the above remarks and amendments, it is respectfully submitted that all claims are in condition for allowance, and such action is earnestly solicited.

No further fee is required in connection the filing of this Amendment. If any additional fees are deemed necessary, authorization is given to charge the amount of any such fee to Deposit Account No. 08-2525.

Respectfully submitted,



Attorney for Applicant(s)
David E. Wildman
(Reg. No. 40,226)
340 Kingsland Street
Nutley, NJ 07110
Telephone (973) 235-6385
Telefax: (973) 235-2363

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